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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2013.03.006.

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High-Dose Chemotherapy and Autologous Stem Cell Transplantation for Nodular Lymphocyte-Predominant Hodgkin Lymphoma

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a distinct subtype of Hodgkin lymphoma that is characterized by unique clinical presentation, histological appearance, and indolent disease course. The recurrent nature of disease provides an opportunity to examine the role of stem cell transplantation in its management. We report here a single-center experience of 26 patients with relapsed NLPHL treated with high-dose chemotherapy and autologous stem cell transplantation between 1990 and 2008. With a median follow-up of 50 months (range, 2-138 months), the 5-year overall and event-free survival were 76% (SE 10%) and 69% (SE 10%), respectively. Our data suggest that high-dose chemotherapy and autologous transplantation should be considered as an option for patients with relapsed NLPHL.

INTRODUCTION

Of the 8000 cases of Hodgkin lymphoma (HL) diagnosed in the United States each year, 5% to 10% are further classified as nodular lymphocyte-predominant HL (NLPHL). Descriptions of NLPHL first appeared in the literature in 1936, with the extent of lymphocyte proliferation in the involved lymph nodes suggestive of an improvement in overall survival [1]. In

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1994, the revised European American classification of lymphoid neoplasms recognized this rare clinico-pathological entity of NLPHL not only on the basis of lymphocyte predominance but also on the presence of larger atypical, $CD20^{-}$ positive cells known as *lymphocyte-predominant* cells, previously called *L & H cells* or *Reed-Sternberg cell variants* [2]. The publication of nearly 2 dozen retrospective series has elucidated clinical features of >1500 cases of HL. Clinical features distinguishing NLPHL from classical HL include a greater male predominance (3:1), older median age at presentation (30 to 40 years), and lower incidence of mediastinal involvement (<15%). Additionally, certain risk factors classically associated with HL (including presence of B symptoms, elevated erythrocyte sedimentation rate, bulky disease, and multiple sites of nodal involvement) are less prevalent [1].

The majority of patients present with limited-stage disease with response rates to primary therapy exceeding 90%. Ten percent to 35% of patients relapse after achieving an initial complete remission, however, with a median time to first relapse of 3 to 6 years [1]. Data have shown that those with early unfavorable and advanced stages of NLPHL have outcomes similar to those with classical HL. Although not evidence based, the treatment of advanced-stage NLPHL typically includes rituximab in combination with either Adriamycin, cyclophosphamide, vincristine, decarbazine (ABVD) or cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), given that the malignant cells of NLPHL express the CD20 antigen [3-5]. Such therapy is associated with long-term remissions in many, but eventually some patients will relapse. At present, there is no uniform data on the outcome of second-line therapy, as there is no consensus on which type of treatment should be used. Furthermore, the role of autologous stem cell transplantation (ASCT) in this setting remains poorly described. In this study, we report our experience with ASCT for patients with relapsed NLPHL.

METHODS

The selected study population included 26 patients with relapsed NLPHL who underwent high-dose chemotherapy and autologous transplantation at the University of Texas MD Anderson Cancer Center between January 1990 and December 2008. Data were collected from an institutional database of blood and marrow transplantation recipients and from review of patient records. The institutional review board approved this retrospective review. All pathology specimens were reviewed by pathologists at MD Anderson to ensure concordance with the WHO 2008 criteria. According to the WHO 2008 guidelines, NLPHL is characterized by the presence of a nodular proliferation of scattered neoplastic cells, known as *lymphocyte-predominant* cells, occurring in a background of non-neoplastic lymphocytes and histiocytes infiltrating a network of follicular dendritic cells. Of the 26 patients, 8 (31%) were noted to have transformation of their disease to large-cell lymphoma (LCL) at the time of relapse [6].

Responsiveness to therapy was assessed using the International Workshop Criteria published in 1999 [7]. Patients were recognized either as having a complete response, partial response, stable disease, or progressive disease. They were also classified on the basis of chemosensitivity, with those with either partial response or complete response before transplantation defined as being "chemosensitive."

Probabilities of outcomes were calculated utilizing the Kaplan-Meier method. Both overall survival (OS) and event-free survival (EFS) were measured in months, starting from the date of transplantation. EFS indicated the time to disease relapse, progression, or death independent of cause.

RESULTS AND DISCUSSION

Patient characteristics are summarized in Table 1. At the time of transplantation, 9 patients (35%) were in complete response, 13 patients (50%) were in partial response, and 4 patients (15%) had stable disease or progressive disease. At the time of transplantation, 18 patients (70%) had histology consistent with NLPHL, and 8 (30%) had evidence of transformation to LCL. Seven of 18 patients (39%) who were histologically proven to have NLPHL at the time of relapse had advanced disease at the time of initial diagnosis, as compared with 6 of 8 (75%) with ultimate transformation to LCL. At the time of relapse, the vast majority of patients with both NLPHL and transformed LCL had advanced-stage disease: 17 of 18 patients (94%) with NLPHL and 8 of 8 (100%) with transformed disease. Although lactate dehydrogenase values were not available in all patients at relapse, it was elevated in 3 of 10 (30%) patients with NLPHL and 2 of 7 (29%) with transformed LCL. Seven patients (27%) had the presence of B symptoms at the time of transplantation. Pretransplantation lactate dehydrogenase was elevated in 10 of 22 patients (38%). Median age at time of transplantation was 35 years (range, 13-51).

Median number of prior chemotherapy regimens was 3 (range, 1-4), and 12 patients (46.2%) were treated with involved field radiation therapy before transplantation. Fourteen patients (53.8%) received rituximab; 4 in the first-line setting, 11 in the salvage setting, and 9 as a part of their conditioning regimen before transplantation.

The median duration of time from the initial diagnosis to autologous transplantation was 35.2 months (range, 9.2-

Table 1
Patient Characteristics (N = 26)

Characteristic	Value
Age, yrs, median (range)	35 (13-51)
Sex	
Male	24 (92.3)
Female	2 (7.7)
Stage at diagnosis	
I	5 (19.2)
II	6 (23)
III	9 (34.6)
V	5 (19.2)
Unknown	1 (3.8)
B symptoms	7 (26.9)
No. prior chemotherapy regimens, median (range)	3 (1-4)
Prior radiation therapy	12 (46.2)
Prior rituximab	14 (53.8)
Disease status at transplantation	
Complete remission	9 (34.6)
Partial remission	13 (50)
Stable disease	1 (3.8)
Progressive disease	3 (11.5)
Median (range) duration from time of diagnosis to time of autotransplantation, mo	35.2 (9.2-439.4)
Chemosensitivity	
Chemosensitive	22 (84.6)
Chemoresistant	4 (15.3)
Stem cell source	
Bone marrow	3 (11.5)
Peripheral blood	23 (88.4)
Lactate dehydrogenase at transplantation	
Abnormal	10 (38.5)
Conditioning regimen	
BEAM-R	10 (38.5)
BEAM	5 (19.2)
CBV	6 (23)
Other*	5 (19.2)
Histology at transplantation	
NLPHL	18 (69.2)
Large-cell lymphoma	8 (30.7)

BEAM-R indicates carmustine, etoposide, cytarabine, melphalan, and rituximab; BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, and etoposide; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.
Data are presented as n (%) unless otherwise indicated.
* Includes busulfan/melphalen, mitoxantrone/etoposide/thiotepa, BEAM-R/Zevalin, BEAC (carmustine, etoposide, cytarabine, melphalan, and cyclophosphamide).

439.4 months). Conditioning regimens used in order of frequency, from highest to lowest, were R-BEAM (rituximab, carmustine, etoposide, cytarabine, and melphalan), CBV (cyclophosphamide, carmustine, and etoposide), and BEAM (carmustine, etoposide, cytarabine, and melphalan). The remaining 5 patients were treated with various other conditioning regimens. Peripheral blood stem cells were used as a stem cell source in 23 (86%) patients. All patients engrafted after transplantation.

Following transplantation, 22 patients were in complete remission. No treatment-related mortality or treatment-related myelodysplastic syndrome and/or acute myelogenous leukemia occurred in any of the patients included in the study. Ultimately, 7 patients relapsed. Among them, only one relapsed with diffuse large B cell lymphoma, whereas the remainder had return of their NLPHL. Three out of 4 patients (75%) with chemoresistent disease relapsed, as compared with 4 out of 22 (18%) patients with chemosensitive disease.

As summarized in Table 2 and depicted in Figure 1, the 5-year EFS and OS at a median follow-up period of 50 months (range, 2-138 months) were 69% (SE, 10%) and 76% (SE, 10%), respectively. In patients with chemosensitive disease, the 5-year EFS and OS were 79% (SE 10%) and 82% (SE 10%), respectively. Of the 26 patients in the series, 18 patients had relapse of their original histology of NLPHL at the time of transplantation, and 8 patients transformed to LCL. The 5-year EFS and OS for those with NLPHL were 61% (SE 12%) and 73% (SE 12%), respectively. For those with transformation to LCL at the time of transplantation, EFS and OS were 87% (SE 12%) and 87% (SE 12%) respectively. At the conclusion of the follow-up period, 6 deaths occurred on account of progressive disease.

Although not supported by clinical trial data, patients with relapsed NLPHL are often treated with autologous transplantation. Historically, 2 randomized trials have shown that patients with relapsed HL derive a significant benefit from autologous stem cell transplantation over conventional therapy in regard to freedom from treatment failure, even among those with favorable disease characteristics [5,8,9]. The lack of survival benefit has been attributed to the ultimate transplantation of those with relapsed disease initially assigned to the nontransplanted arm [10]. Literature specifically looking at autologous transplantation in the setting of NLPHL is limited and includes very few patients. Jackson et al. [11] reported a median failure-free survival of 39.2

Table 2
Patient Outcomes (N = 26)

Outcome	Result
Engraftment	
Absolute neutrophil count >500/mm^3	10 (8-33) d
Platelets >20,000/mm^3	10 (7-35) d
Median follow-up, mo (range)	50 (2-138)
Cause of death	
Disease progression, n	6
Nonrelapse mortality, n	0
Event-free survival at 5 yr	69% (SE 10%)
Overall survival at 5 yr	76% (SE 10%)
Chemosensitive patients (n = 22)	
Event-free survival at 5 yr	79% (SE 10%)
Overall survival at 5 yr	82% (SE 10%)
NLPHL (n = 18)	
Event-free survival at 5 yr	61% (SE 12%)
Overall survival at 5 yr	73% (SE 12%)
Large-cell lymphoma (n = 8)	
Event-free survival at 5 yr	87% (SE 12%)
Overall survival at 5 yr	87% (SE 12%)

NLPHL indicates nodular lymphocyte-predominant Hodgkin lymphoma.

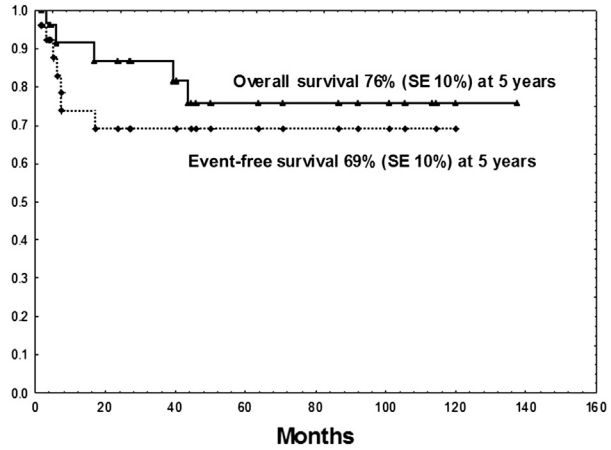

Figure 1. Event-free and overall survival at 5 years. Median follow-up of 50 months (range, 2-138 months).

months (range, 28.6-138.5 months) for NLPHL patients receiving autologous transplantation after achieving PR with standard chemotherapy. Five of 8 patients in their series experienced relapse after transplantation and went on to receive further chemotherapy. Basioli et al. [12] reported 60% OS in 19 patients with NLPHL transformed to LCL. They showed that 9 of 164 patients who received autologous transplantation for NLPHL and transformed to LCL had OS comparable to the 10 transformed patients who received salvage systemic therapies. Bierman et al. [13] reported on 19 patients treated with ASCT for relapsed or refractory NLPHL. Treatment outcomes were compared with 299 patients treated with ASCT for relapsed/refractory nodular sclerosing HL. Both progression-free survival and OS were similar with a 5-year progression-free survival after ASCT for patients with NLPHL of 50% compared to 39% of patients with nodular sclerosis HD ($P = .30$) and a 5-year OS of 56% and 53%, respectively ($P = .36$).

These results, along with our data, suggest that autologous transplantation is a potentially curative option for patients with relapsed NLPHL, particularly in the setting of chemosensitive disease. The low incidence rate of NLPHL precludes the development of prospectively designed randomized clinical trials evaluating the optimal therapeutic approach to this subset of patients. Aside from the limitations inherent to retrospective studies, the small number of patients available for review precluded the development of univariate or multivariate analysis to uncover specific patient characteristics predictive of outcome. The role of rituximab as a part of the conditioning regimen in autologous transplantation also remains unanswered. Following suit with several other diseases, those with chemoresistant disease appear to be a higher risk for relapse following transplantation. In summary, autologous transplantation is a reasonable therapeutic alternative for patients with relapsed or transformed NLPHL.

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Comparison of Characteristics of Bacterial Bloodstream Infection between Adult Patients with Allogeneic and Autologous Hematopoietic Stem Cell Transplantation

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Although autologous and allogeneic hematopoietic stem cell transplantation (HSCT) are fundamentally different procedures, a tailored approach to bacterial bloodstream infection (BSI) according to the type of HSCT has not yet been suggested. We evaluated the characteristics of BSI after HSCT, with a focus on comparison of BSIs between recipients of autologous HSCT (auto-HSCT) and allogeneic HSCT (allo-HSCT). Among 134 patients (59 received allo-HSCT and 75 received auto-HSCT) who underwent HSCT, BSIs were reported earlier in patients who underwent auto-HSCT, compared with those who underwent allo-HSCT (mean 12.1 ± 3.4 days versus 32.8 ± 27.1 days, $P = .006$). Among patients receiving allo-HSCT, post-neutrophil-engraftment bacterial BSI showed an association with grade ≥2 acute graft-versus-host disease (GVHD). In patients who underwent auto-HSCT, results of multivariate analysis showed that not receiving prophylactic antibiotics ($P = .004$) and having elevated serum C-reactive protein ($P = .034$) were risk factors of BSI. Elevated CRP ($P = .01$) and acute GVHD ≥ grade 2 ($P = .002$) were independent risk factors in patients who underwent allo-HSCT. Those differences originated mainly from the impact of acute GVHD-related postengraftment BSIs of patients who underwent allo-HSCT. To establish the best defense strategy against BSI, the distinctive natures of bacterial BSI after HSCT between auto-HSCT and allo-HSCT should be considered.

INTRODUCTION

Bacterial bloodstream infection (BSI) is a common and sometimes fatal event in patients who undergo hematopoietic stem cell transplantation (HSCT). Although advances in HSCT, such as the use of prophylactic antibiotics, reduced-intensity conditioning (RIC), and improved supportive care, have contributed to a substantial reduction of morbidity and mortality, the incidence of bacterial BSI has been reported to range from 20% to 43%, even after the year 2000 [1-4].

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